REMARKS

The Examiner's Office Action of May 17, 2005 has been carefully considered. In the instant application, claims 1-9 are pending. Claims 1-7 are allowed and claims 8-9 are rejected. In view of the above amendment, and the remarks that follow, the reconsideration and withdrawal of the present basis for rejecting the claims herein of this application is respectfully requested.

I. Discussion of the Amendment

Claims 2-7 and 9 are amended to reflect proper antecedent basis and to better and more properly reflect what Applicants regards as their invention. The support for the amendment is found throughout the specification, such as at page 10, line 12 to page 11, line 31.

Claim 8 is cancelled, without prejudice.

Claim 9 is also amended to limit the uses of the compound of the invention to those that are regarded enabled by the Examiner.

Claims 10-19 are added. The support for these claims is found throughout the specification, such as at page 24, line 10 to page 25, line 2.

Applicants reserve the right to pursue the cancelled subject matter of the claims in a subsequent application.

This amendment to the claims adds no new matter.

II. Discussion of the Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

With the above amendment, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim 8 is cancelled, without prejudice. The amended claim 9 is directed to specific uses of the compound of the invention that are regarded enabled by the Examiner, i.e., for treating a cardiovascular diseases, stable or unstable angina pectoris, coronary heart disease, Prinzmetal angina, acute coronary syndrome, heart failure, myocardial infarction, stroke, endothelial dysfunction, atherosclerosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, or renovascular hypertension.

The newly added claim 19 is directed to a specific use of the compound of lowering cardiovascular risk of postmenopausal women or after intake of a contraceptive. As the Examiner has failed to specifically address why this use is not enabled by the specification, Applicants assume that claim 18 satisfies the enablement requirement.

The newly added claims 10-18 are directed to specific uses of the compound of the invention for treating thrombosis, peripheral artery occlusive disease, diabetes or a diabetes complication, nephropathy, retinopathy, chronic glomerulonephritis, chronic renal failure, osteoporosis, restricted memory performance or a restricted ability to learn, or erectile dysfunction, respectively. Applicants submit herewith the following references published prior to the priority date of April 24, 2003, of the present application that evidence the disease states/conditions claimed to be treatable by upregulating the expression of the enzyme endothelialnitric oxide (NO) synthase:

- Thrombosis - M. T. Gewaltig et al., *Cardiovascular Research*, vol. 55, p. 250 - 260, 2002 (Exhibit A), in section 3.2 entitled "Antiplatelet effect of NO" at pages 252 and 253, discusses the inhibiting action of NO and NO donors on platelet aggregation, which plays a major role in the formation of thrombi., and in Figure 5 at page 255, the antiaggregatory effect is listed among the effects caused by NO which can be mediated by influencing eNOS expression.

- Peripheral artery occlusive disease - K. Ouriel, *Lancet*, vol. 358, p. 1257 - 1264, 2001 (Exhibit B), in the section of "Pathophysiology" at pages 1258-1259, states that peripheral arterial disease develops on the basis of atherosclerotic lesions and NO has been shown to reduce leucocyte adhesion to endothelium.

- Diabetes, a diabetes complication, nephropathy or retinopathy – M. S. Goligorsky et al., *Hypertension*, vol. 37, p. 744 - 748, 2001 (Exhibit C), in Figure 5 at page 747, illustrates that advanced glycation end-products, as are increasingly formed in diabetic states, lead to an inhibition of eNOS expression and NO production which in turn leads, among others, to vascular damages and in particular to nephropathy; at the first paragraph of the right column at page 747, states that "All these sequels of eNOS/NO deficiency have clear-cut relevance to the progression of diabetic nephropathy"; and in the section "Conclusions" at page 747, states that "Shifting the emphasis from N-deacetylase to the eNOS/NO system may have important implications for the therapy of diabetic complications, including diabetic nephropathy".

- Chronic glomerulonephritis and chronic renal failure – P. A. Ortiz et al., *American Journal of Physiology, Regulatory, Integrative and Comparative Physiology*, vol. 284, p. R628 - R638, 2003 (Exhibit D), at page R628, states that, in the kidney, NO regulates salt and fluid reabsorption, hemodynamics, renin secretion and tubuloglomerular feedback; and in Figure 2 at page R631 the role of NO synthase isoforms along the nephron is displayed.

- Osteoporosis – (1) K. E. Armour et al., *Endocrinology*, vol. 142, p. 760 - 766, 2001 (Exhibit E), at page 765, states that the experimental results show that eNOS is essential for normal osteoblast function and that eNOS deficiency is associated with reduced bone mass and an impaired anabolic response to high does estrogen; (2) M. Hukkanen et al., *Bone*, vol. 32, p. 142 - 149, 2003 (Exhibit F), in the Abstract, states that NO may modulate estrogen anabolic effects on bone homeostasis by restraining osteoclast-mediated bone resorption and stimulation of osteoblast activity; and (3) S. J. Wimalawansa, *Journal of Bone and Mineral Research*, vol. 15, p. 2240 - 2244, 2000 (Exhibit G), at page 2244, states that NO donor therapies may have the potential to emerge as a new group of potent, effective, and economical agents in preventing (and possibly treating) menopausal bone loss, particularly as an alternative therapy for estrogen.

- Restricted memory performance or a restricted ability to learn – (1) S. Haul et al., Journal of Neurophysiology, vol. 81, p. 494 - 497, 1999 (Exhibit H), in the "Introduction" section at page 494, states that inhibition of NO synthase has been shown to suppress long-term potentiation (LTP) both under in vivo and in vitro conditions, and that eNOS is the primary source of NO in the postsynaptic neuron during LTP; and (2) N. Doreulee et al., Brain Research, vol. 964, p. 159 - 163, 2003 (Exhibit I), in the Abstract, states that NO is a retrograde messenger involved in the process of learning and memory, and possibly endothelial NO synthase participates in neuronal modulation processes.

- Erectile dysfunction - A. Burnett, *Drugs of Today*, vol. 36, p. 155 - 162, 2000 (Exhibit J), in the second paragraph of the left column at page 158, discusses the significance of the nitric oxide cascade in erectile function and states that, besides neuronal NOS, also endothelial NOS has been localized within the penis and is perceived to provide an auxiliary source of nitric oxide for the production of penile erection.

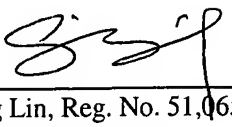
In view of the aforesaid noted references and the fact that the Examiner has not cited any documentary evidence to refute Applicants' support, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

III. In Conclusion

In view of the above amendment and remarks, it is respectfully submitted that the present application is in condition for allowance. Early notice to this effect is, thus, respectfully requested.

The Commissioner is hereby authorized to charge the fee required and any additional fees that may be needed to Deposit Account No. **18-1982** in the name of Aventis Pharmaceuticals Inc.

Respectfully submitted,



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